Heart Failure Research Review™

Making Education Easy

Issue 66 - 2022

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Abbreviations used in this issue:

BNP/NT pro-BNP = (N-terminal prohormone of) brain natriuretic peptide; **CV** = cardiovascular; **ED** = emergency department; **HF** = heart failure; **HFPEF/HFREF** = HF with preserved/reduced ejection fraction; **HR** = hazard ratio; **LVEF** = left ventricular ejection fraction; **MRA** = mineralocorticoid receptor antagonist; **NYHA** = New York Heart Association; **RAAS** = renin-angiotensin-aldosterone system; **RCT** = randomised controlled trial; **RFA** = radiofrequency ablation; **SGLT** = sodium-glucose cotransporter.

Welcome to issue 66 of Heart Failure Research Review.

This issue begins with the SODIUM-HF trial, published in the Lancet, reporting no reductions in clinical events in ambulatory patients with HF assigned to a low-sodium diet. Other research included in this issue identified a number of surrogate markers of gut dysfunction that were associated with HF severity and outcomes. There is also a report of a novel septostomy device for percutaneous RFA-based interatrial shunting for HFPEF. This issue concludes with a meta-analysis of trial data reporting a lower risk of hyperkalaemia and no increased risk of hypokalaemia associated with SGLT-2 inhibitor use in patients with type 2 diabetes at high CV risk or with chronic kidney disease.

Thank you for all the comments and suggestions you have sent – they are appreciated so please keep sending them.

Kind Regards,

Professor John Atherton
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Reduction of dietary sodium to less than 100 mmol in heart failure (SODIUM-HF)

Authors: Ezekowitz JA et al., on behalf of the SODIUM-HF Investigators

Summary: The open-label SODIUM-HF trial randomised adults receiving optimally tolerated medical therapy for HF (NYHA class II–III) to a low-sodium diet (<1500 mg/day; n=397) or usual care (n=409). There was no significant difference between the low-sodium versus usual care group for the composite clinical outcome of all-cause mortality and CV-related hospitalisations or ED visits at 12 months (15% vs. 17%; HR 0.89 [95% CI 0.63–1.26]) or for its components of all-cause mortality (6% vs. 4%; 1.38 [0.73–2.60]), CV-related hospitalisation (10% vs. 12%; 0.82 [0.54–1.24]) and CV-related ED visits (4% vs. 4%; 1.21 [0.60–2.41]).

Comment: The evidence to support sodium restriction in HF has been based on observational analyses and small RCTs with conflicting results. SODIUM-HF aimed to address this knowledge gap. The intervention group achieved a significant reduction in sodium intake (median intake 1658 vs. 2286 mg/day); however, this did not translate into a significant reduction in CV hospitalisation/ED visits or all-cause mortality. While improvements in symptoms and quality of life were noted, these were unblinded evaluations. Overall, this study suggests that strict sodium restriction beyond the usual advice to limit salt intake is unlikely to have a significant effect on morbidity or mortality in ambulatory patients with HF on top of contemporary medical therapy.

Reference: Lancet 2022;399:1391–400
Abstract

Effectiveness and cost-effectiveness of an empowerment-based self-care education program on health outcomes among patients with heart failure

Authors: Yu DS et al.

Summary: Patients aged ≥55 years with HF (NYHA class II–IV) were randomised to an empowerment-based education programme of self-care assessments, goal-orientated actions in symptom recognition and response, fluid and dietary modification and lifestyle management (n=118) or an education control group (n=118) in this trial from China. Compared with controls, the empowerment programme was associated with significantly greater improvements in Self-care Heart Failure Index management score (mean difference, 13.76 [95% CI 5.89–21.62]) and symptom perception score (20.36 [13.98–26.75]), as well as reduced risks of ED visits (incidence rate ratio, 0.55 [0.31–0.95]) and hospital admissions (0.38 [0.21–0.68]), and significant improvements in self-care knowledge and confidence. The empowerment programme was also found to be cost effective.

Comment: Self-care is a critical component of disease management and a recognised prognostic marker in patients with chronic HF. This study demonstrated improved self-care following a group-delivered, empowerment-based education programme in patients recently diagnosed with HF. While there were additional costs associated with delivering the programme, these costs were recovered by decreased healthcare utilisation. If confirmed by others, this model of care could be applied within current HF disease management programmes.

Reference: JAMA Netw Open 2022;5:e225982
Abstract

Association of left atrial structure and function with heart failure in older adults

Authors: Inciardi RM et al.

Summary: The reference range of left atrial measures and their associations with NT-proBNP level and the related risk for incident HF or death were evaluated for 4901 Atherosclerosis Risk In Communities study participants without prevalent HF. According to the study's reference limit, left atrial abnormalities were evident in ~20% of the participants. A multivariate analysis revealed that each left atrial measurement was associated with NT-proBNP level and, except for left atrial maximal volume, incident HF or death, with consistent results in participants with a normal left atrial maximal volume (p>0.05 for interaction). Left atrial measures were prognostic for incident HFPEF or death and incident HFREF or death. The prognostic accuracy of HF risk factors and NT-proBNP level was significantly improved by the addition of left atrial measures except left atrial maximal volume.

Comment: Increased left atrial size has previously been reported to be associated with worse outcomes. In this large community-based cohort, left atrial minimal volume and measures of left atrial function were stronger predictors of incident HF or death than the standard measure of maximal left atrial volume. Indeed, these measures were predictive of both HF with a reduced or preserved LVEF. While these findings are promising, their applicability to clinical practice will be limited, as these are not standard measures obtained in most echocardiographic laboratories. Furthermore, future studies are required to determine whether such measures will allow for early intervention to prevent or delay the development of HF.

Reference: J Am Coll Cardiol 2022;79:1549–61
Abstract

Electronic alerts to improve heart failure therapy in outpatient practice

Authors: Ghazi L et al.

Summary: Patients with HFREF were randomised by provider to receive an electronic best practice alert that sent information on guideline-directed medical therapy recommendations and patient characteristics to their provider (n=685) or no alert (control group; n=625) at the time of an outpatient visit; at baseline, 84% of the participants were receiving β-blockers, 71% RAAS inhibitors, 29% MRAs and 11% SGLT2 inhibitors. Compared with the control group, a greater proportion of participants assigned to the best practice alert group met the primary outcome of an increase in the number of prescriptions for drug classes that complied with guideline-directed medical therapy at 30 days (26% vs. 19% [p=0.03]) with 14 patients needed to alert for the addition of one guideline-directed drug class. When providers were surveyed, 79% agreed that the alert was effective.

Comment: Prior studies have reported that most changes to therapy in patients with chronic HF occur in the acute care setting. Despite there being a number of effective disease-modifying therapies, they are often not started or uptitrated in the ambulatory care setting. The PROMPT-HF study demonstrated that personalised alert triggers applied through an electronic health record improved prescription rates (especially for β-blockers) compared with usual care in patients attending cardiology and internal medicine outpatient clinics. While it is likely that this approach will be context-specific, it represents a relatively low-cost intervention to improve the uptake of guideline-directed medical therapy.

Reference: J Am Coll Cardiol 2022;79:2203–13
Abstract

Surrogate markers of gut dysfunction are related to heart failure severity and outcome

Authors: Israr MZ et al., on behalf of the BIOSTAT-CHF investigators

Summary: The role of biomarkers of gut dysfunction in assessment and risk stratification of HF was explored using data from 1783 patients with worsening HF enrolled in the BIOSTAT-CHF cohort. The researchers identified significant associations of carnitine-TMAO (trimethylamine-N-oxide) pathway metabolites, namely acetyl-L-carnitine, γ-butyrobetaine, L-carnitine and TMAO, as well as TFF-3 (trefoil factor-3) with a composite outcome of 3-year HF hospitalisation or all-cause mortality (HRs 2.04–2.93 [p≤0.002]). A graded association was seen when the carnitine-TMAO pathway metabolites and TFF-3 were combined as a gut dysfunction panel, with a greater number of elevated markers significantly associated with higher NYHA class, higher plasma BNP levels and worse outcomes (HRs 1.90–4.58 [p≤0.008]). Prediction of the aforementioned composite outcome was also significantly improved when gut dysfunction biomarkers were added to the contemporary BIOSTAT HF risk model.

Comment: The gut microbiota comprises trillions of micro-organisms producing thousands of metabolites. This study adds to earlier reports regarding the prognostic utility of gut-derived metabolites, by demonstrating graded associations for carnitine metabolites and the gut peptide TFF-3 with adverse outcomes in patients with HF. These data provide further support for a gut-heart axis in patients with HF; however, intervention studies are required to determine whether this is a causal association.

Reference: Am Heart J 2022;248:108–19
Abstract

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- Frailty, guideline-directed medical therapy and outcomes in HFREF

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- Dietary sodium reduction in heart failure patients
- Oral anticoagulants reduce the risk of dementia
- Avocado consumption reduces risk of cardiovascular disease

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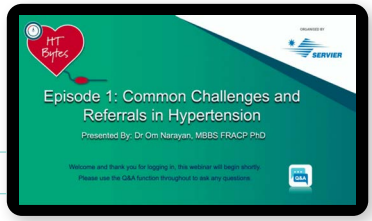

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Alirocumab after acute coronary syndrome in patients with a history of heart failure

Authors: White HD et al., for the ODYSSEY OUTCOMES Investigators

Summary: This *post hoc* analysis of the ODYSSEY OUTCOMES study compared outcomes for participants with versus without a history of HF who had been randomised to receive alirocumab or placebo for recent acute coronary syndrome treated with concomitant intensive or maximally tolerated statins. Overall, 2815 (14.9%) of the study's 18,924 participants had a history of HF. Alirocumab was found to reduce LDL (low-density lipoprotein) cholesterol and lipoprotein(a) levels irrespective of HF history, whereas the significantly reduced rate of major adverse CV event in the alirocumab versus placebo arm (HR 0.85 [95% CI 0.78–0.93]) persisted in participants with no HF history (0.78 [0.70–0.86]), but not in those with a history of HF (1.17 [0.97–1.40]; p=0.0001 for interaction). Hospitalisations for HF were not reduced in the alirocumab arm for the entire study population, for the subgroup with a history of HF or for those without a history of HF.

Comment: In this *post hoc* analysis from the ODYSSEY OUTCOMES study, despite similar LDL-cholesterol lowering, patients with a history of HF did not benefit from PCSK9 inhibition, with no reduction in major adverse CV events or HF hospitalisations. While this should be regarded as hypothesis generating, these findings accord with prior HF RCTs evaluating the efficacy of statin therapy and suggest that clinical outcomes are mostly driven by nonatherosclerotic mechanisms in patients with HF.

Reference: Eur Heart J 2022;43:1554–65
Abstract

Evaluation of the causes of sex disparity in heart failure trials

Authors: Morgan H et al.

Summary: These researchers analysed data from 248,620 participants from 146 HF trials to explore differences according to sex. They found that the median proportion of female participants was 25.8%. The proportion of female participants was particularly low for trials enrolling patients with ischaemic cardiomyopathy (17.9%) or severe systolic dysfunction (21.4%) and those involving an invasive procedure (21.1%), whereas the highest proportions were seen in studies in participants with HFPEF (51.6%) and older participants (40.5%). The prevalence of female trial participants was significantly lower than the population prevalence across all LVEF categories (25.8% vs. 49.0% [p<0.01]).

Comment: This study explored possible explanations for why male patients have predominated in HF clinical trials. While biological variation may contribute to the lower prevalence of women in trials enrolling patients with HF due to ischaemic heart disease, clinical trial enrolment criteria may also drive selection bias in some HFREF studies. Nonetheless, even following adjustment for LVEF, women remain under-represented in studies evaluating invasive treatments including implantable devices. As stated by the authors, this highlights the need to review trial designs and recruitment strategies to ensure all eligible patients have the same chance of being enrolled in clinical trials.

Reference: Heart; Published online March 31, 2022
Abstract

The RAISE trial: a novel device and first-in-man trial

Authors: Sun W et al.

Summary: The safety and efficacy of a novel atrial septostomy device for percutaneous radiofrequency ablation (RFA)-based interatrial shunting in HFPEF was assessed in a preclinical study in 11 normal domestic pigs and a first-in-human study in 10 patients with HFPEF; the procedure was performed successfully in both studies. A left-to-right interatrial shunt was created in the pigs with a mean defect size of 5.5mm and without any procedure-related safety events and seven of the pigs exhibiting continuous shunting at 6 months with a mean defect size of 4.1mm. In the patients with HFPEF, a median interatrial defect diameter of 5.0mm was measured immediately, and again there were no major safety events, including deaths or thromboemboli. Seven patients exhibited continuous shunting with a defect size of 4.0mm at 6 months, at which time eight of the patients had a significant reduction in NT-proBNP level of 2149 pg/mL (p=0.028), a significant 88m increase in 6-minute walk distance (p=0.008) and improvements in NYHA functional class.

Comment: There remain limited treatment options for patients with HFPEF. The RAISE trial explored the feasibility, safety and preliminary efficacy of percutaneous RFA-based atrial shunting as a means to decrease left atrial pressure and avoid the potential thrombotic risks of an implantable device. While the recently reported REDUCE LAP-HF II trial failed to achieve its primary endpoint using an implantable shunt device, it did provide important insights to guide the design of future clinical trials evaluating atrial septostomy, including the need to avoid enrolling patients with raised pulmonary vascular resistance during exercise. We await the results of these planned studies.

Reference: Circ Heart Fail 2022;15:e008362
Abstract

Therapeutic targets for heart failure identified using proteomics and Mendelian randomization

Authors: Henry A et al.

Summary: These researchers evaluated associations of 90 CV proteins with HF using fixed-effect meta-analysis of data from four population-based studies with 3019 participants and 732 HF events. Causality of HF-associated proteins was then investigated using analyses of genome-wide association studies in >30,000 individuals. Forty-four of the proteins were found to be significantly positively associated with incident HF risk, of which increased CSF-1 (macrophage colony-stimulating factor 1), Gal-3 (galectin-3) and KIM-1 (kidney injury molecule 1) showed evidence of a causal positive association, while increased ADM (adrenomedullin), CHI3L1 (chitinase-3-like protein 1), CTSL1 (cathepsin L1), FGF-23 (fibroblast growth factor 23) and MMP-12 (matrix metalloproteinase-12) showed evidence of causal protection. It was noted that there are clinical trials currently evaluating agents targeting ADM and Gal-3, and that with the exception of KIM-1, all the others are potential druggable targets.

Comment: Substantial progress has been made in the management of HF; however, outcomes remain poor, so there is interest in identifying novel therapeutic targets. This interesting study integrated population-based proteomic and genomic data to identify eight candidate proteins with a likely causal association with incident HF. They then identified that seven of these eight candidate proteins could be targeted by drugs, including two proteins (ADM, Gal-3) in which phase 2 clinical trials are underway in patients with HF or hypertension. While this provides a template to prioritise novel disease targets, future studies should also explore broader populations, coupled with more detailed evaluation of HF phenotypes (e.g. reduced or preserved LVEF).

Reference: Circulation 2022;145:1205–17
Abstract

Sodium-glucose cotransporter 2 inhibitors and risk of hyperkalemia in people with type 2 diabetes

Authors: Neuen BL et al.

Summary: This was a meta-analysis of individual participant data from six RCTs (n=49,875) together evaluating four SGLT-2 inhibitors in individuals with type 2 diabetes who were at high risk of CV disease or had chronic kidney disease, and in whom routine serum potassium level data were available. Serious hyperkalaemia developed in 1754 of the participants and there were 1119 investigator-reported hyperkalaemic events recorded. The risk of serious hyperkalaemia was lower with SGLT-2 inhibitor use (HR 0.84 [95% CI 0.76–0.93]), as was the incidence of investigator-reported hyperkalaemic events (0.80 [0.68–0.93]) with the effects consistent across studies (respective p values 0.71 and 0.21 for heterogeneity) and across subgroups according to baseline kidney function, HF history and RAAS, diuretic or MRA use. There was no significant increase in the risk of hypokalaemia with SGLT-2 inhibitor use (HR 1.04 [95% CI 0.94–1.15]; p=0.42 for heterogeneity).

Comment: Hyperkalaemia is a well-recognised complication of RAAS inhibitors. This individual, patient-level data analysis from RCTs enrolling patients with type 2 diabetes reported that SGLT-2 inhibitors decreased the risk of serious hyperkalaemia, with no significant increase in hypokalaemia. There was no heterogeneity for treatment effect in different populations (including patients with HF), with similar findings if the two RCTs evaluating patients with HF and a reduced LVEF were included. Coupled with their morbidity/mortality benefits, this provides a strong case for including SGLT-2 inhibitors early in the HF treatment pathway.

Reference: Circulation 2022;145:1460–70
Abstract

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Independent commentary by Professor John Atherton

Professor John Atherton is the Director of Cardiology at the Royal Brisbane and Women's Hospital, Professor, University of Queensland and Adjunct Professor, Queensland University of Technology. He previously chaired the Asia-Pacific Acute Decompensated Heart Failure Registry SAC and the CSANZ Heart Failure Council. He has been an appointed member of the Australian Government Medical Services Advisory Committee and sat on the National Heart Foundation Heart Failure Guidelines executive writing group. Research interests include investigating novel methods to detect presymptomatic cardiac disease and cardiac genetics. Contributions to statewide service enhancement include coordinated heart failure disease management and co-establishing a cardiac genetics service.